REGULATORY PROJECT MANAGER
LABELING REVIEW

DRUG: Zoloft (sertraline hydrochloride) 25 mg, 50 mg, and 100 mg Tablets and 20 mg/mL Oral Solution
NDA 018939/S-100 (tablets) and 020990/S-057 (oral solution)
Sponsor: Pfizer, Inc.
Indication: Treatment of major depressive disorder (MDD), obsessive compulsive disorder (OCD), panic disorder (PD), Post-traumatic stress disorder (PTSD), social anxiety disorder (SAD), and premenstrual dysphoric disorder (PMDD)

Pending and recently approved Labeling Supplements:

NDA	Supplement	Dated	Provides for	Status
018939	S-091 and S-093	6/8/17 and 6/30/17	Addition of rhabdomyolysis to Postmarketing Experience and addition of new subsection to W&P entitled QTc Prolongation/ (b) (4)	Approved 12/8/17
020990	S-049 and S-050	6/8/17 and 6/30/17	Addition of rhabdomyolysis to Postmarketing Experience and addition of new subsection to W&P entitled QTc Prolongation (b) (4)	Approved 12/8/17
018939	S-100	7/7/21	o Add reference to the change under RMC in Highlights o Add Sexual Dysfunction in Warnings and Precautions o Add "Sexual Dysfunction" to Patient Counseling Information (section 17). o Add "Sexual problems (dysfunction)" to the Medication Guide o Replace language in the Overdosage Section (10)	Pending
020990	S-057	7/7/21	o Add reference to the change under RMC in Highlights o Add Sexual Dysfunction in Warnings and Precautions o Add "Sexual Dysfunction" to Patient Counseling Information (section 17). o Add "Sexual problems (dysfunction)" to the Medication Guide o Replace language in the Overdosage Section (10)	Pending
[redacted]				(b) (4)

BACKGROUND

- On May 10, 2018, the Agency received a Citizen's Petition (CP, docket # FDA-2018-P-1846) from Data Based Medicine Americas, Ltd., requesting that FDA immediately revise all SSRI and SNRI labeling.
- After a careful collaborative review between DP, DUOG and OSE it was decided that the labels for SSRI (selective serotonin reuptake inhibitors) /SNRI (serotonin norepinephrine reuptake inhibitors) would be revised, and Safety Labeling Change (SLC) Notifications were issued on June 7, 2021. The letters required Applicants to incorporate labeling language pertaining to the association between use of these drugs with the occurrence of sexual dysfunction.
- In addition, the Agency requested revisions to the Overdosage Section (10).
- The sponsor agreed to the requested revisions.
- This review will only include pending supplements 018939/S-100 and 020990/S-057, and not the other pending supplements listed above.

REVIEW

CBE: Yes
Reviews:

- Safety and Clinical Memo (E. Zerislassie, M. Stone, T. Farchione) dated 5/28/21 (entered in DARRTS under NDA 018936 Prozac)
- Office of Prescription Drug Promotion (D. Shah) review dated 5/11/21 (entered in DARRTS under NDA 018936 Prozac)
- Division of Medical Policy Programs/Patient Labeling (S. Hutchins) review dated 5/11/21(entered in DARRTS under NDA 018936 Prozac)

These supplements provide for revisions to the prescribing information and Medication Guide to align with the SLC letter we issued on 6/7/21.

- These supplements propose the following changes to the PI and MG for sertraline:
  - Add reference to the change under RMC in Highlights
  - Add Sexual Dysfunction in Warnings and Precautions (section 5.11).
  - Add "Sexual Dysfunction" to Patient Counseling Information (section 17).
  - Add "Sexual problems (dysfunction)" to the Medication Guide
  - Replace language under Section 10 Overdosage

DISCUSSION

1. Applicant submitted labeling included a cross reference to 5.11 in Section 6.1, Table 3. Also included was a change to the storage statement in Section 16.
2. The Agency recommended removal of the cross reference, alternatives to the storage statement wording, and additional minor formatting changes.
3. The Applicant confirmed agreement with the Agency's proposals on 8/27/21.

CONCLUSIONS

1. These CBE labeling supplements only provide for the revisions as stated above when compared to the last approved labeling (approval letter dated 12/8/17).
2. The sponsor has incorporated our revisions, as stated in the Agency's SLC letter dated 6/7/21.
3. I recommend that an approval letter issue for these pending supplemental applications.

{See appended electronic signature page}

LCDR Ann Sohn, PharmD, MS
Regulatory Project Manager

{See appended electronic signature page}

Kimberly Updegraff, RPh, MS
Associate Director of Labeling

Attachment: annotated labeling, agreement email

33 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page.

Sohn, Ann J

From: Zerislassie, Ermias
Sent: Tuesday, September 14, 2021 1:20 PM
To: Sohn, Ann J
Subject: FW: [EXTERNAL] RE: NDA 19839 and NDA 20990 Zoloft 7/7/21 submission

Concurrence email

From: Erika Fernandez <Erika.Fernandez@viatris.com>
Sent: Friday, August 27, 2021 1:41 PM
To: Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Subject: [EXTERNAL] RE: NDA 19839 and NDA 20990 Zoloft 7/7/21 submission

CAUTION: This email originated from outside of the organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>

Hi Ermias

Viatris agrees with the revisions for Zoloft's USPI proposed by the Division.

Have a great weekend

Thank you

Erika

From: Zerislassie, Ermias <Ermias.Zerislassie@fda.hhs.gov>
Sent: Thursday, August 19, 2021 10:16 AM
To: Erika Fernandez <Erika.Fernandez@viatris.com>
Subject: NDA 19839 and NDA 20990 Zoloft 7/7/21 submission

CAUTION: This email originated from outside of the company. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Good Morning Erika,

Please see our comments in the attached label that was submitted on 7/7/21. Please provide a response by 8/27/21.

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To exercise your rights or make a request concerning the processing of your Personal Data, you may contact us by emailing us at dataprivacy@Viatris.com.
Thank you.

Please think before you print. View in other languages.

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/s/

ANN J SOHN
09/20/2021 09:26:05 AM

KIMBERLY S UPDEGRAFF
09/26/2021 11:28:59 PM

NDA 018936

LABELING REBUTTAL ACCEPTED

Eli Lilly and Company
Attention: Richard D. Hoffmann, MS, RAC
Advisor, Global Regulatory Affairs - US
Lilly Corporate Center, Drop code 2543
Indianapolis, IN 46285

Dear Mr. Hoffmann:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Sarafem (fluoxetine hydrochloride) capsules.

On June 7, 2021, we sent you a letter invoking our authority under section 505(o)(4) of the FDCA to require safety related labeling changes to the labeling of Sarafem to address the risk of sexual dysfunction. The decision to require safety labeling changes was based on new safety information about this risk identified since this product was approved. You were directed to submit, within 30 days of the date of that letter, a supplement proposing changes to the approved labeling or to notify FDA that you do not believe a labeling change is warranted and submit a rebuttal statement detailing the reasons why such a change is not warranted.

We acknowledge receipt of your rebuttal statement dated July 2, 2021, detailing the reasons why you believe a labeling change to address the risk of sexual dysfunction is not warranted for Sarafem.

We have completed the review of your rebuttal statement and agree that no labeling change is warranted at this time to address the new safety information described above because marketing of Sarafem capsules was discontinued in 2010 and the premenstrual dysphoric disorder (PMDD) indication was withdrawn in 2015.

If you have any questions, call Meredith Hillig, MS, Safety Regulatory Project Manager, at (301) 796-1218.

Sincerely,

{See appended electronic signature page}

Catherine Sewell, M.D., M.P.H.
Deputy Director for Safety Division of Urology, Obstetrics, and Gynecology
Office of Rare Diseases, Pediatrics, Urologic, and Reproductive Products
Center for Drug Evaluation and Research

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/s/

CATHERINE A SEWELL
08/12/2021 05:01:16 PM

Clinical Review

To:

NDA#	DARRTS SDN	EDR#	Document Type	Letter Date	Received Date
018936	1709	0139	Rebuttal to SLCN	7-2-2021	7-2-2021

Through: Christina Chang, M.D., M.P.H., Team Leader, DUOG
Catherine Sewell, M.D., M.P.H., Deputy Director for Safety, DUOG

From: Marcea Whitaker, M.D., Medical Officer, DUOG

Date: August 12, 2021

Re: Rebuttal to SLCN for SSRI/SNRI Class labeling for association with sexual dysfunction

Applicant: Eli Lilly and Company

Background:
Following a joint review by the Division of Psychiatry and DUOG, a safety labeling change notification (SLCN) was sent to all NDA holders on June 7, 2021. The SLCN requested changes in the labeling for all SSRIs/SNRIs to add a Warning (and corresponding changes in highlights of the Prescribing Information, Section 17 Patient Counseling Information, and the Medication Guide) regarding SSRI/SNRI-associated sexual dysfunction in males and females. The Applicant has submitted a rebuttal to the SLCN and believes the requested changes are not warranted.

At the time of the November 28, 2000 approval of the premenstrual dysphoric disorder (PMDD) indication for fluoxetine hydrochloride capsules (proprietary name Sarafem to distinguish from Prozac), PMDD was managed by the Division of Psychiatry. The oversight of the PMDD indication was subsequently moved to DUOG. The Applicant subsequently discontinued marketing of Sarafem capsules and the Premenstrual Dysphoric disorder (PMDD) indication was removed from the labeling of fluoxetine HCl capsules.

Current Submission:
The Applicant provided the following regulatory history for Sarafem under NDA 18936. Our review of documents in DARRTS verified the history below:

Date	Regulatory Action
November 28, 2000	Sarafem pulvule (capsules) approval for PMDD (10 mg and 20 mg)

June 10, 2010 (SN0026, General Correspondence)	Applicant notified FDA of voluntary discontinuation of the marketing for Sarafem 10 mg and 20 mg capsules for business reasons, not safety or efficacy reasons
June 10, 2010 (SN0027, General Correspondence)	Letter to Orange Book Staff requesting removal of both capsule strengths
June 10, 2010	FDA Delisting of Sarafem from Drug Registration and Listing System (DRLS)
February 8, 2011	FDA acknowledged marketing withdrawal of Sarafem capsules under NDA 18936
May 13, 2014	FDA issued SLCN for SSRIs regarding the risk of angle-closure glaucoma
June 3, 2015	FDA issued SLCN for SSRIs regarding the risk of serotonin syndrome
June 30, 2015 (SN0078)	Applicant submitted rebuttal statement to SLCNs, indicating that the requested labeling changes were not warranted because the Applicant proposed to remove the PMDD indication from Sarafem labeling and that the marketing for Sarafem capsules had ceased
July 20, 2015	Posting of Sarafem discontinuation in the Federal Register
November 24, 2015	FDA approved the Change-Being-Effected (CBE) Supplement for withdrawal of PMDD indication. In the letter, the FDA also stated that the Applicant was not required to implement safety labeling changes as requested for previously for Sarafem

Conclusions and Recommendation:
The Applicant has provided adequate justification in the rebuttal to show that the requested changes regarding sexual dysfunction in the Sarafem labeling are not warranted. The marketing of Sarafem capsules was discontinued in 2010 and the PMDD indication was removed from product labeling in 2015.

DUOG will issue a regulatory letter to the Applicant, concurring with the rebuttal and agreeing that the safety labeling changes requested in the June 7, 2021 letter are not necessary.

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/s/

CHRISTINA Y CHANG
08/12/2021 04:58:06 PM
Also signing on behalf of Dr. Marcea Whitaker

CATHERINE A SEWELL
08/12/2021 05:00:39 PM

Kalsi, Jasmeet (Mona)

From: Kalsi, Jasmeet (Mona)
Sent: Friday, July 16, 2021 10:41 AM
To: hoffman_richard_d@lilly.com
Subject: NDA 018936 Information Request
Attachments: Information_Request_for_additional_studies_fluoxetine.docx

Good Morning Richard,

I am a project manager in the Division of Psychiatry and the division is requesting the attached information for NDA 018936.

Please let me know if you have any questions.

Thank you,
Mona

Jasmeet (Mona) Kalsi, PharmD, RAC
LCDR, United States Public Health Service
Regulatory Project Manager

Center for Drug Evaluation and Research
Office of Regulatory Operations
Division of Regulatory Operations for Neuroscience
Psychiatry Group

U.S. Food and Drug Administration
Tel: (240) 402-8977
Jasmeet.Kalsi@fda.hhs.gov

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Please refer to your New Drug Application (NDA 018936) submitted under section 505(b) of the Federal Food, Drug and Cosmetic Act for PROZAC (fluoxetine) oral tablets.

The efficacy of pharmacologic treatments in pediatric major depressive disorder (MDD) remains unclear, as the majority of placebo-controlled randomized trials of antidepressant medications have not demonstrated a significant benefit of treatment over placebo. FDA is currently exploring several factors that may contribute to the high rate of negative and failed trials, including study design, placebo response, and antidepressant exposure-response. FDA plans to conduct several quantitative analyses by pooling data from adult and pediatric MDD programs. Leveraging relevant, available clinical data may provide further insight for future development programs and may inform regulatory-decision making.

To further expedite this process, we ask that you submit the following adult datasets that include the pertinent efficacy and safety information listed below from phase 2 and 3 studies. If you have previously submitted the requested longitudinal data in electronic format, please provide the Division with the Serial Number or eCTD Sequence Number. We would like to have the requested data in electronic format by 09/30/2021, and we understand some data may not be available for all studies. If our requested date is not feasible, please provide an alternative date for submitting the data.

Table 1: List of Requested Efficacy Information

MDD Efficacy Data
Unique Subject ID
Study ID
Site ID
Country
Treatment Group
Gender
Age
Race
Height
Weight
Body Mass Index
Study Completion Status
Study Discontinuation Reason and Date
Duration of Current MDD Episode
Number of Previous Episodes

Dose
Received previous cognitive therapy?
Ongoing cognitive therapy?
Response to cognitive therapy?
Previous use of antidepressants?
Response to previous antidepressants?
Age of Onset
Comorbid anxiety? (y/n)
Comorbid ADHD? (y/n)
Other comorbid psychiatric disorders? (y/n)
Concomitant medications
Visit Number
Visit Date
Randomization Date
Nominal Study Week/Day
Number of Days on Treatment
MADRS Itemized Data
MADRS Total Score
HAMD Itemized Data
HAMD Total Score
CDRS-R Itemized Data
CDRS-R Total Score
Clinical Global Impression Scale – Severity
C-SSRS Itemized Data
History of Suicidal Ideation? (y/n)
History of Suicidal Behavior? (y/n)
Pharmacokinetic Data*
Primary Caregiver information
Healthcare utilization Data

Table 2: List of Requested Safety Information

MDD Safety Data
Unique Subject ID
AE Body System or Organ Class
AE Dictionary-Derived Term
End Date of Adverse Event - numeric
Study Day of End of Adverse Event
Outcome of Adverse Event
Serious Event

Severity/Intensity
Start Date of Adverse Event - numeric
Study Day of Start of Adverse Event
Reported Term for the Adverse Event
Duration (Days)
Actual Treatment, Study Specific Dose

*Please include any population pharmacokinetic or population pharmacokinetic-pharmacodynamic models that you developed to characterize the pharmacokinetics in adults and pediatrics

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/s/

JASMEET K KALSI
07/16/2021 11:22:33 AM

Medical Officer's Consultation:
Adverse Effects of SSRIs and SNRIs on Male Sexual Function

From:	Roger Wiederhorn, MD, Medical Officer Division of Urology, Obstetrics and Gynecology
	Mark S. Hirsch, MD, Medical Team Leader, DUOG
	Catherine Sewell, MD, MPH, Deputy Director of Safety, DUOG
To:	Sarah Seung, Regulatory Project Manager Division of Psychiatry (DP)
Drug Classes:	selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs)
Date consult requested:	August 27, 2018
Date consult completed:	June 9, 2021

1. Background

On May 10, 2018, the Agency received a Citizen's Petition (CP) from Data Based Medicine Americas, Ltd requesting that FDA immediately revise all SSRI and SNRI labels as follows:

- Add WARNINGS, PRECAUTIONS, and HIGHLIGHTS OF PRESCRIBING INFORMATION to inform that the use of, and withdrawal from, SSRIs and SNRIs can result in "genital anesthesia", "pleasureless or weak orgasm", "delayed or absent orgasm", "loss of libido", "erectile dysfunction", "decreased vaginal lubrication", "reduced nipple sensitivity", "flaccid glans penis during erection", "reduced response to sexual stimuli", "decreased capacity to experience sexual pleasure", and "persistent genital arousal disorder (PGAD)".

- Add WARNINGS, PRECAUTIONS, HIGHLIGHTS OF PRESCRIBING INFORMATION, and a BOXED WARNING to inform that sexual side effects can sometimes persist for years or indefinitely after discontinuation of the drug; that they can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.

The Petitioner also requests FDA to issue a notification letter requiring a REMS of all manufacturers of SSRIs and SNRIs. Specifically, the Petitioner requests that FDA require manufacturers to take the following actions:

- Send a Dear Health Care Provider letter to psychiatrists, psychologists, internists, family practitioners, urologists and endocrinologists informing them that these drugs have serious adverse reactions (as described above) and pose a significant public health concern; and

- Develop a Medication Guide and Communication Plan to make patients aware that the drugs have serious risks (as described above) that could affect the patient's decision to use or to continue to use the product.

FDA has approved the following seven SSRIs:

1. Celexa (citalopram),
2. Lexapro (escitalopram),
3. Paxil (paroxetine),
4. Prozac (fluoxetine),
5. Trintellix (vortioxetine),
6. Viibryd (vilazodone), and
7. Zoloft (sertraline).

FDA has approved the following four SNRIs:

1. Cymbalta (duloxetine),
2. Effexor XR (venlafaxine),
3. Fetzima (levomilnacipran), and
4. Pristiq (desvenlafaxine).

Additionally, there are many abbreviated new drug applications (ANDAs) approved for SSRIs and SNRIs.

The Petitioner states that current labeling does not adequately convey the breadth, severity or potentially permanent nature of the adverse sexual effects from SSRI and SNRI products. The Petitioner states that neither patients nor health care professionals can reasonably be expected to know the full impact of the products on sexual functioning that could include "profound genital numbness" and "the loss of ability to experience pleasure during orgasm", and therefore it is not possible for patients to weigh the benefits of treatment against the harms of SSRIs and SNRIs.

Currently, all SSRIs and SNRIs contain at least some language regarding adverse effects on sexual function. However, none of the SSRIs or SNRIs contain a Boxed Warning regarding adverse sexual effects.

The Office of Regulatory Policy (ORP) consulted the Division of Psychiatric Products (DP) to address the issues raised by the Petitioner. Subsequently, DP consulted DUOG to evaluate reports of sexual adverse effects in males and females receiving SSRIs and SNRIs. This consultation report concerns sexual adverse effects in men only.

The consult question to DBRUP (same question for both males and females) is:

1. Please assess the strength of available evidence that SSRIs and SNRIs cause any of the following adverse events (a) while on treatment, and (b) following discontinuation of treatment with an SSRI/SNRI. Discuss the duration of persistence, if such information is

available. You may combine items in this list if you consider them to be describing the same clinical phenomena.

a. Genital anesthesia
b. Pleasureless or weak orgasm
c. Delayed or absent orgasm
d. Loss of libido
e. Erectile dysfunction
f. Reduced nipple sensitivity
g. Flaccid glans penis during erection (if this is distinct from erectile dysfunction)
h. Reduced response to sexual stimuli
i. Decreased capacity to experience sexual pleasure
j. Persistent genital arousal disorder (defined in petition as an uncontrollable and relentless feeling of physiological arousal in the genitals but without any accompanying feeling of sexual desire)

2. Consultant's Review of the Available Evidence

In responding to the consult question, we sought to evaluate the strength of the available evidence that SSRIs and SNRIs cause the sexual adverse effects listed above (in men), whether as on-treatment adverse effects or as adverse effects that arise or persist after stopping treatment. We did so by evaluating 1) evidence from controlled clinical studies, and 2) evidence from the postmarketing experience. This section summarizes the available evidence and our evaluation.

2.1 Summary of Evidence from Controlled Clinical Studies

We first assessed the strength of evidence to support the various sexual adverse effects based on results from randomized, placebo-controlled studies. For this analysis, we conducted a survey of the labels of SSRI and SNRI drugs. We sought to determine whether the current SSRI and SNRI labels contain mention (in any fashion) of the 10 sexual adverse effects described by the Petitioner.

We chose the following Preferred Terms (PTs) for tabulating our survey results because these PTs are widely recognized, broad categories of sexual adverse effects that might contain the 10 specific sexual adverse effects described by the Petitioner: Ejaculatory Disturbance (Table 1), Libido Decreased (Table 2), Orgasmic Disturbance (Table 3), Erectile Dysfunction (Table 4), and Sexual Dysfunction (Table 5).

When specific adverse reaction terms were identified in the product labels, those specific adverse reaction terms are shown in the respective tables. If the drug was used for multiple indications, the adverse reaction data (e.g., incidences) shown for the overall population was used. If data in the overall population was not available in the labels, data for the subpopulation with major depressive disorder was used. Blank rows indicate no reporting of the PT in the label for that product.

Table 1: Ejaculatory Disturbance

NDA Drug	Active	Placebo
	SSRIs	
018936 Prozac		
019839 Zoloft	Ejaculatory failure 8%	1%
020031 Paxil	13 to 15%	0 to 2%
021519 Luvox	Delayed ejaculation 8%	1%
020822 Celexa	Ejaculation delay 6%	1%
021323 Lexapro	Ejaculation delay 12%	1%
022567 Viibryd		
204447 Trentellix		
	SNRIs	
020151 Effexor	Abnormal ejaculation 12%	0%
021427 Cymbalta	Ejaculation delayed 2%	1%
021992 Pristiq Incidences shown for 50mg, 100mg, 200mg and 400 mg, respectively	Ejaculatory delay: 1%, 5%, 7%, 6% Ejaculatory disorder: 0%, 1%, 2%, 5% Ejaculation failure: 1%, 0%, 2%, 2%	<1% 0% 0%
022256 Savella (indicated for fibromyalgia)	Ejaculation disorder and ejaculatory failure >2%, and at a rate > placebo	
021411 Strattera (indicated for attention deficit disorder) Incidences shown from clinical trials in adults	Ejaculation disorder or ejaculation delayed 4%	1%
018207 Desyrel		

Source: Reviewer's Survey and Tabulation of Approved SSRI and SNRI Labels

Consultant's Comment: Treatment with SSRIs and SNRIs affects ejaculation – the effect is described in labeling mostly as "ejaculatory delay" or as "ejaculatory failure". This effect is observed for both SSRIs and SNRIs.

Table 2: Libido Decreased

Drug	Active	Placebo
	SSRIs	
018936 Prozac		
019839 Zoloft	Libido decreased 6%	2%
020031 Paxil	Libido decreased 0 to 9%	0 to 2%
021519 Luvox	Libido decreased 2%	1%
020822 Celexa	Libido decreased 3.8%	<1%
021323 Lexapro	Libido decreased 6%	2%
022567 Viibryd Incidences shown for 20 mg and 40 mg, respectively	Libido decreased 3% and 4%	<1%
204447 Trentellix		
	SNRIs	
020151 Effexor	Libido decreased 2%	0%
021427 Cymbalta	Libido decreased 3%	1%
021992 Pristiq Incidences shown for 50mg, 100mg, 200mg and 400 mg doses, respectively	Libido decreased 0%, 3%, 5% and 8%	0%
022256 Savella	Libido decreased >2%, and at rate > placebo	
204168 Fetzima		
021411 Strattera (indicated for attention deficit disorder) Incidences shown from clinical trials in adults	Libido decreased 3%	1%
018207 Desyrel		

Source: Reviewer's Survey and Tabulation of Approved SSRI and SNRI Labels

Consultant's Comment: Treatment with SSRIs and SNRIs affects libido – the effect is described in labeling almost uniformly as "libido decreased". This effect is observed for both SSRIs and SNRIs.

Table 3: Orgasmic Disturbance

Drug	Active	Placebo
	SSRIs	
018936 Prozac		
019839 Zoloft		
020031 Paxil		
021519 Luvox	Anorgasmia 2%	1%
020822 Celexa		
021323 Lexapro	Anorgasmia 3%	<1%
022567 Viibryd Incidences shown for 20 mg and 40 mg, respectively	Anorgasmia/Abnormal orgasms 2% and 2%	0%
204447 Trentellix		
	SNRIs	
020151 Effexor	Orgasmic disturbance 2%	0%
021427 Cymbalta	Orgasm abnormal 2%	<1%
021992 Pristiq Incidences shown for 50mg, 100mg, 200mg and 400 mg doses, respectively	Orgasm abnormal 0%, 1%, 2% and 3% Anorgasmia 0%, 3%, 5% and 8%	0% 0%
022256 Savella		
204168 Fetzima		
021411 Strattera		
018207 Desyrel		

Source: Reviewer's Survey and Tabulation of Approved SSRIs and SNRIs

Consultant's Comment: Treatment with SSRIs and SNRIs may affect orgasm, <u>but</u> the evidence for orgasmic dysfunction is not extensive (Table 3), and not nearly as compelling as the evidence for ejaculatory delay/ejaculatory failure and decreased libido (Tables 1 and 2). Based solely on this survey of labeling, it remains unclear as to what specific clinical events were reported as "anorgasmia" and "abnormal orgasm". Some of these "anorgasmia" and "abnormal orgasm" events probably reflect ejaculatory delay/ejaculatory failure and are not true "anorgasmia" or 'abnormal orgasm" events.

Table 4: Erectile Dysfunction

Drug	Active	Placebo
	SSRIs	
018936 Prozac		
019839 Zoloft	Erectile dysfunction 4%	1%
020031 Paxil all RCTs	Erectile dysfunction 2 to 9%	0-3%
021519 Luvox	Erectile dysfunction 2%	1%
020822 Celexa	Erectile dysfunction 3%	<1%
021323 Lexapro	Erectile dysfunction 2%	<1%
022567 Viibryd Incidences shown for 20 mg and 40 mg, respectfully	Erectile dysfunction 0% and 3%	<1%
204447 Trentellix		
	SNRIs	
020151 Effexor	Erectile dysfunction 6%	0%
021427 Cymbalta	Reported only in non MDD and GAD pts	
021992 Pristiq Incidences shown for 50mg, 100mg, 200mg and 400 mg doses, respectively	Erectile dysfunction 3%, 6%, 8%, 11%	1%
022256 Savella	Erectile dysfunction >2% and at rate > placebo	
I204168 Fetzima Incidences shown for 20mg, 40mg, 80mg and 120 mg, respectively	Erectile dysfunction 6% overall and 0%, 6%, 8%, 10%, respectively	2%
021411 Strattera (indicated for attention deficit disorder) Incidences shown from clinical trials in adults	Erectile dysfunction 8%	1%
018207 Desyrel		

Source: Reviewer's Survey and Tabulation of Approved SSRIs and SNRIs

Consultant's Comment: Treatment with SSRIs and SNRIs affects erectile function – though not as much as it affects ejaculation and libido - the effect is described in labeling uniformly as "erectile dysfunction". This effect is observed for both SSRIs and SNRIs.

Table 5: "Sexual Dysfunction"

Drug	Active	Placebo
	SSRIs	
018936 Prozac		
019839 Zoloft		
020031 Paxil		
021519 Luvox		
020822 Celexa		
021323 Lexapro		
022567 Viibryd		
204447 Trentellix (RCTs) Incidences shown for 5mg, 10mg, 15mg and 20 mg, respectively	3%, 4%, 4% and 5%	2%
20447 Trentellix (ASEX with sexual dysfunction at baseline) Incidences shown for 5mg, 10mg, 15mg and 20 mg, respectively	16%. 20%, 19%, and 29%	14%
	SNRIs	
020151 Effexor		
021427 Cymbalta		
021992 Pristiq Incidences shown for 50mg, 100mg, 200mg and 400 mg, respectively	1%, 0%, 0%, 2%	0%
022256 Savella		
204168 Fetzima		
021411 Strattera		
018207 Desyrel		

Source: Reviewer's Survey and Tabulation of Approved SSRIs and SNRIs

Consultant's Comment: "Sexual dysfunction" is a vague, overly general term that did not yield much information in this survey.

Consultant's Comment: It is noted that none of the labels contained any mention of alterations in penile sensation. If such alterations do occur, they must occur very infrequently.

2.2 Evidence from Postmarketing Experience

Postmarketing experience also provides evidence about the sexual adverse effects of SSRIs and SNRIs. For this part of the consultation, we did not evaluate post-marketing experience for ejaculatory delay / ejaculatory failure, decreased libido, or erectile dysfunction because these on-treatment sexual adverse effects appeared evident from controlled clinical studies. Instead, we

evaluated the postmarketing experience for 1) alterations in penile sensation, and 2) sexual adverse effects that persisted or arose after stopping SSRI or SNRI therapy.

For this part of the consultation, we reviewed evidence from three sources:

1) A survey of recent Periodic Adverse Experience Reports (PADERs) or Periodic Safety Update Reports (PSURs) for several SSRIs and SNRIs, and
2) Post-marketing experience information as provided by the Division of Pharmacovigilance (DPV) in their June 5, 2019, draft consultation report, and
3) Post-marketing experience information as provided by the Petitioner.

2.2.1 Postmarketing Experience Information for Altered Penile Sensation

2.2.1.1 Survey of PADERs / PSURS for Altered Penile Sensation

Recent PADERs or PSURs for several SSRIs or SNRIs were surveyed for adverse event terms relating to altered penile sensation. The search terms used to query these periodic reports were: penile sensation, hypoesthesia (penile), genital sensation, numbness (genital) and genital sensitivity.

- Paxil (paroxetine): In PSUR September 8, 2012 to September 2017, there were no positive responses to the queries.
- Zoloft (sertraline): In PADER April 1, 2017 to March 31, 2018, there were no positive responses to the queries
- Effexor (venlafaxine): In PADER December 29, 2011 to December 28, 2012, there were no positive responses to the queries
- Lexapro (escitalopram): In Annual ADER August 14, 2016 to August 2017, there were no positive responses to the queries
- Cymbalta (duloxetine): In PSUR August 4, 2014 to August 3, 2017, there were no positive responses to the queries
- Pristiq (desvenlafaxine): In PADER March 1, 2017 to February 28, 2018, there were no positive responses to the queries

2.2.1.2 Information Provided by DPV for Altered Penile Sensation

In their June 6, 2019, draft consult, DPV stated that FAERS data suffers from underreporting. Thus, FAERS data is not useful for calculating the incidence of a specific AE. These FAERS limitations, coupled with the high background rates of sexual dysfunction in the general and depressed populations, make FAERS data a poor source to determine the association between the occurrence of any specific sexual dysfunction (such as altered penile sensation) in patients using SSRIs/SNRIs.

> ***Consultant's Comment: One case illustrates some of the limitations of spontaneous reports: We refer to FAERS Case #13380384, in which the patient reported decreased sensitivity of his genitals at zero (0) minutes after starting paroxetine. As the case narrative continues, the patient reports persistence of decreased genital sensitivity at 8 months following drug discontinuation. This case illustrates some of the difficulties associated with clinical interpretation of spontaneously reported sexual adverse events.***

2.2.1.13 Information Provided by the Petitioner for Altered Penile Sensation

- The Petitioner provide a discussion of neurophysiological tests conducted in patients with premature ejaculation who were treated with clormipramine (a non-SSRI or SNRI) or with fluoxetine. With clormipramine, there were significant differences observed in sensory thresholds, suggesting clormipramine increases the sensory threshold for genital stimulation. In the fluoxetine study, which was placebo-controlled, penile sensory thresholds were increased as compared to placebo. However, in neither study did patients report "genital anesthesia" or decreased genital sensation.
- The Petitioner cited postmarketing reports and articles, usually of single cases, of patients taking SSRIs or SNRIs who experienced decreases or changes in genital sensation to touch. In none of the cases was there a complete absence of sensation either by clinical detail or by neurological testing. Some patients noted a decrease in, or lack of, pleasurable experience in response to genital touch. Other patients experienced decreased excitement, arousal, or pleasure in response to genital touch.

Consultant's Comment: While there are many reports of "numbness" in other body parts, as well as reports of "emotional numbness" in patients taking SSRIs and SNRIs, reports specific to alteration of genital sensation are rare. In their draft consult report, DPV suggested that this may reflect a more general, "sexual arousal disorder" and not a local neurophysiological genital effect. In this circumstance, DPV concludes that penile anesthesia is a misnomer.

2.2.2 Postmarketing Experience Information For Persistent Sexual Adverse Effects

Most of the information in this section comes from the June 6, 2019, DPV draft consult report. In this section, information is presented in the following categories:

1) Information from an FDA search of FAERS for cases of persistent sexual adverse effects in patients who took SSRIs or SNRIs.
2) Information from clinical studies for persistent sexual adverse effects in patients who took SSRIs or SNRIs
3) Information from published literature articles cited by the Petitioner for persistent sexual adverse effects in patients who took SSRIs or SNRIs

2.2.2.1 Information from FAERS for Cases of Persistent Sexual Adverse Effects

DPV performed a thorough FAERS search that sought to identify cases reporting persistent sexual dysfunction that arose in patients on SSRIs or SNRIs and persisted following SSRI/ SNRI discontinuation, or a sexual dysfunction that arose following discontinuation of SSRIs/ SNRIs.

DPV identified a total of 104 cases where sexual dysfunction arose in patients actively taking SSRIs or SNRIs and persisted after drug discontinuation, and a total of 25 cases where sexual dysfunction arose after SSRIs or SNRIs were discontinued. Thus, a total of **129 cases** were identified in the search.

A total of 91 of the 129 identified cases were males, and of the male cases, 16 cases arose following cessation of SSRI/ SNRI therapy.

The patient age ranged from 17 to 71 years with an average age of 34 years.

A total of 91 of the 129 cases (71%) were initially received by FDA from 2010 through 2018, although the DPV draft consult reports no initial cases received in 2010 or 2017. A total of 63 of the 129 cases (49%) were submitted as expedited reports. A total of 20 of the 129 cases (16%) referenced persistent sexual dysfunction information from the literature, found on the internet, or heard in an internet chat room.

The most commonly reported antidepressant in this case series was sertraline (n=25), which, according to DPV, was the top selling antidepressant among SSRIs/SNRIs in males and females across all age groups in 2017-2018. Citalopram (n=21), fluoxetine (n=21), venlafaxine (n=20), escitalopram (n=16), paroxetine (n=11), and duloxetine (n=8) all followed sertraline. Bupropion, desvenlafaxine, and vortioxetine were each reported in three or fewer cases. Concomitant use of two or more antidepressants was reported in some cases.

The time to onset of the sexual adverse effect after initiating SSRI or SNRI therapy was not reported in 92 of the 129 cases (73%). Of the 37 cases that did report the time to onset of a sexual adverse effect, a total of 15 cases reported the sexual adverse effect arising within 7 days of initiating the SSRI or SNRI, with some cases reporting the sexual adverse effect arising on the same day as starting the SSRI or SNRI, or within 1 to 2 days of receiving the first dose. Some cases reported the time to onset of the sexual adverse effect as "almost immediately," "with starting," "directly upon taking," "right after starting," "immediately after starting," and "within days". The remaining 22 cases reported the time to onset of the sexual adverse effect of less than 7 days to less than 1 month (n=6), less than 1 month to less than 1 year (n=7), and less than 1 year (n=2).

In terms of the total duration of SSRI or SNRI therapy, the total duration of SSRI or SNRI therapy was not reported in 33 of the 129 total cases (26%). Of the 96 cases that reported the total duration of SSRI or SNRI therapy, less than 7 days (n=4), greater than 7 days to less than 1 month (n=9), greater than 1 month to less than 1 year (n=40), greater than 1 year to less than 5 years (n=30), greater than 5 years (n=12), and "40-50 pills" (n=1) were reported.

In terms of duration of persistence of the sexual adverse effect after discontinuation of the SSRI or SNRI, duration of persistence of the sexual adverse effect was not reported in 66 of the 129 total cases (51%). Of the 63 cases that reported the duration of persistence of the sexual adverse effect after discontinuing SSRI or SNRI therapy, the sexual adverse effect persisted for less than 7 days (n=1), greater than 7 days to less than 1 month (n=1), greater than 1 month to less than 1 year (n=24), greater than 1 year to less than 5 years (n=29), and greater than 5 years (n=8).

In terms of improvement in the sexual adverse effect following discontinuation of the SSRI or SNRI, 12 of the 129 total cases (14%) described an improvement in the sexual adverse effect following discontinuation of the SSRI or SNRI, and 6 of the 129 cases (7%) described resolution of the sexual adverse effect post-discontinuation. In terms of the extent of improvement, some cases reported a full resolution while others reported a partial resolution. An example of partial resolution is provided here: "Premature ejaculation appears to have completely resolved, the very low libido and sensitivity to pleasure down below and during orgasm hasn't resolved, although it

has improved" [FAERS case #10651273]). In terms of time to onset of improvement, when reported, time to onset of improvement was most commonly reported as weeks to months post-discontinuation of SSRI or SNRI therapy.

DPV observed that multiple potential confounding factors were reported in among this case series. For example, depression and anxiety were the most commonly reported indications for antidepressant SSRI/SNRI use in the case series. DPV noted that both depression and anxiety are confounders because they themselves cause sexual dysfunction. History of antidepressant use or current concomitant use of two or more antidepressants was reported in approximately 16% of the cases. DPV observed that other confounders reported in the case series included: divorce or relationship issues, diabetes mellitus, sleep disorder or chronic fatigue, seizure disorder, concomitant medication other than antidepressants or herbal medications, multiple sclerosis, hypertension, hypogonadotrophic hypogonadism, smoking, and a history of genital injury. Some cases reported more than one confounder.

DPV further observed that several cases reported a psychiatric history other than depression, anxiety or obsessive compulsive disease (OCD). For example, one case reported a diagnosis of chronic traumatic encephalopathy, post-concussion syndrome, ADHD, and PTSD in addition to major depressive disorder. This patient also described experiencing delusions and paranoia and said he "…was used in military experiments illegally without my consent by the same doctors who abused me with this medication that hurt me. I was used in human radiation experiments and had CIA mind control tactics used on me" (FAERS Case #10642466). In another case, the patient stated she had "…borderline personality disorder and complex post-traumatic stress disorder" (FAERS Case #10072145).

In terms of reported adverse events other than sexual adverse effects, 92 of the 129 total cases (71%) reported adverse events (AEs) other than sexual adverse effects. In many cases, multiple adverse events were reported, including one case that reported more than 36 adverse events AEs, including, but not limited to, sexual adverse events. In many cases, non-sexual adverse events AEs, including withdrawal symptoms, were reported concurrently or in close temporal proximity to the onset of the sexual adverse event. For example, in one case, the following was reported: *"…the patient experienced the following symptoms after slowly lowering the dose and after stopping venlafaxine on unspecified dates: dizziness, nausea, brain zaps - like lightning zaps/electric shocks in different areas of the head, headaches, fatigue, body ache, tearful and crying for a long time and for no apparent reason, irritable and agitated, shivers, flu-like feelings, diarrhea, addiction to buying things, craving foods, insomnia, felt very weak, stressed out, life not seeming real, high cholesterol, sexual dysfunction, fidgety, feeling inferior, difficult to think and remember information, confusion and unable to mentally focus. The patient further developed sensitivity to sound, felt hot and also felt very cold at times, felt like his brain was expanding through his skull which was very painful, legs shook whilst sitting down, feet turned purple, saw flashes, cold chills, sweating, giddy, lack of sleep, vigilance issues - did not always feel safe especially when having to cross roads, did not seem to mentally register what he saw, change in personality, excess fluid and wax feeling in ears and had the urge to clean ears with cotton buds, he once banged on a door without knowing that he was (doing so), unable to cope with any type of stress or changes as they made him extremely weak and emotionally upset, emotions changed quickly from anger to upset, weight gain during withdrawal and went to about*

130kg, after stopping began to lose weight and depression due to suffering all the above symptoms" (FAERS Case #7625032, 2011, Foreign, Expedited)."

As part of their FAERS search methodology, DPV also sought to identify cases that reported persistent sexual adverse effects that arose in patients following discontinuation of SSRI or SNRI therapy and persisted. In this search, DPV identified twenty-five (25) cases that were reported to emerge after discontinuation of SSRI or SNRI therapy, but not while receiving treatment. These cases commonly lacked clinical details. In most of these cases, use of SSRI/ SNRI therapy was for at least six months, and in six cases, use of SSRI/ SNRI therapy was for at least seven years. In most of these cases, multiple adverse events AEs in addition to sexual dysfunction AEs were reported. In ten of these cases, sexual adverse effects were reported to persist for a year or longer. In five of these cases, the sexual adverse effect was reported to improve or to "wax and wane."

Finally, DPV classified the 129 total cases into four broad categories of sexual dysfunction based on the apparent chief or most severe complaint in the case narrative. The four broad categories of sexual dysfunction that were employed by DPV for this exercise were: "*Libido disorder*", "*Orgasmic disorder*", "*Arousal disorder*" and "*Erectile disorder*". Using this categorization scheme, cases were most commonly assigned to "*Libido disorder*" (n=44), followed by "*Orgasmic disorder*" (n=32), "*Arousal disorder*" (n=17), and "*Erectile disorder*" (n=15). DPV acknowledged significant overlap amongst these 4 broad categories because many cases reported more than one type of sexual adverse effect. DPV also categorized 21 cases as "*Unspecified*" because in these cases, DPV could not identify the patient's chief or most severe complaint due to lack of clinical details.

For illustrative purposes, DPV provided the following 3 case narratives as examples of "*Libido disorder*", "*Arousal disorder*" and "*Erectile disorder*", respectively:

A case of "Libido disorder"
FAERS Case #11446878 (2015, U.S., Non-expedited, duloxetine) describes a 61-year-old male who received duloxetine for the treatment of depression. "Almost immediately" after initiating duloxetine, he experienced decreased libido. Approximately a year and a half later he began tapering duloxetine with the goal of discontinuing it since he was now in a relationship and the decreased libido was an issue. An unknown time after decreasing the duloxetine dose he experienced "withdrawal symptoms" described as "brain shiver and static in his head, vertigo, dizziness, dry mouth, discomfort and at times felt very warm." The decreased libido did not resolve during the taper down. Duloxetine was discontinued. The case stated that "the events persisted" four weeks after discontinuation.

A case of "Arousal disorder"
FAERS Case # 9531502 (2013, Foreign, venlafaxine) describes a 26-year-old male patient who received venlafaxine for the treatment of depression. He stated, "from day one it nullified my interest in sex and sexual thoughts were scarce and hard to focus on." He was no longer interested in intercourse. He also reported a lack of morning erections and "fleeting" stimulated erections unless "constantly supported by stimuli or caressing." His "ability to sense pleasure was also significantly lower." Orgasms were no longer satisfying and pleasurable. The patient

discontinued venlafaxine "cold turkey." He still reported erectile difficulties and low libido leaving him "indifferent towards finding a sexual partner." He reported "sexual thoughts and fantasies require focus and are hard to maintain." During intercourse, he states a lot of time and stimulation are required to feel the level of arousal he was accustomed to prior to receiving venlafaxine. After approximately five months his orgasm quality returned, the outcomes of the other sexual adverse effects were not reported

A case of "Erectile disorder"

FAERS Case # 6688134 (2008, U.S., Expedited, fluoxetine) describes a 29-year-old male who received fluoxetine beginning at age 18 during a time in which he reported anxiety and uncertainty related to his academics and professional future. He reported that prior to initiating fluoxetine he had "never had problems getting erections; he had full and lasting erections from erotic thoughts or visual stimuli; regular nocturnal and morning erections and was easily aroused." A few days after initiating fluoxetine he reported "impotence, no nocturnal erections, and lack of erection without physical stimuli". Ejaculation difficulty was also reported; however, he reported his libido was unaffected. After four months, he discontinued fluoxetine abruptly without experiencing any withdrawal signs or symptoms. He stated that erectile dysfunction (ED) has persisted for 11 years. No other psychological or physical health problems were reported. A penile Doppler ultrasound showed arterial blood flow to the penis was "extremely good" and a dynamic infusion cavernosometry study showed no leakage from the penile veins. A somatosensory evoked potential study indicated no problems with his spine. Alprostadil self-injection therapy has allowed penetrative sex, however, he states that "intercourse must be prearranged". He has maintained a long-term, stable relationship and reported a positive vocational adjustment.

DPV summarized their analysis of "persistent" sexual adverse effects following SSRI/ SNRI therapy as follows:

> The difficulties of interpreting data from sources other than from prospective, randomized, placebo-controlled studies confound the ability to make meaningful conclusions for the following reasons:
>
> - Sexual dysfunction is a highly prevalent problem worldwide. 31% of men in the U.S. general population report problems with sexual functioning. In one survey of U.S. men, sexual dysfunction response items included:
>   - Lacking desire for sex
>   - Arousal difficulties
>   - Difficulty achieving orgasm or ejaculation
>   - Anxiety about sexual performance
>   - Climaxing or ejaculating too quickly
>   - Pain with intercourse
>   - Not finding sex pleasurable
> - Studies have consistently demonstrated higher rates of sexual dysfunction in patients with depressive or anxiety disorders.
> - Severely depressed patients may not be consciously aware of a sexual dysfunction until they begin to respond to therapy, creating uncertainty about whether the sexual dysfunction is drug or improvement related. Careful pre-treatment screening for sexual dysfunction was not documented in many of the data sources in the Petition.

Consultant's Comment: It is relevant to highlight that in most cases, clinical details describing the course of the patient's' psychiatric illnesses after discontinuation of the SSRI/ or SNRI were not reported. Therefore, it is not possible to make an assessment as to whether the cause of the improvement in, or resolution of, the sexual dysfunction might have been due to a concurrent improvement in their psychiatric illnesses.

2.2.2.2 Information from Clinical Studies for Persistent Sexual Adverse Effects

No is information available from placebo-controlled studies to evaluate the persistence of sexual adverse effects that arose either while on SSRIs or SNRIs and persisted after the medication was stopped, or arose after medication was stopped and persist.

Consultant's Comment: Data from controlled clinical studies often provides the best evidence of a relationship between a reported adverse event and drug therapy. Unfortunately, no evidence is available from controlled clinical studies to inform our determination of relatedness for "persistent" sexual adverse events associated with SSRI/ SNRI therapy.

2.2.2.3 Information from Articles Cited for Persistent Sexual Adverse Effects

In some of the articles, case information was gleaned from solicited reporting using guided questions. In one article, patients were eliminated from inclusion in a non-predefined manner. In other articles, spontaneous reports of anecdotal experience were detailed. In most of the articles, background rates of sexual dysfunction were not considered. In most of the articles, there was no documentation of systematic follow-up of the sexual adverse effects of concern.

Consultant's Comment: While there are reports of sexual dysfunction that arose while men were on SSRI/ SNRI therapy and persisted after discontinuation, as well as reports of sexual dysfunction that arose in men after discontinuation of SSRI/ SNRI therapy and persisted; in most of these cases, multiple clinical confounders are present and clinical detail is lacking. No additional evidence is available from controlled clinical studies to better inform a causality determination. Overall, the available evidence is considered inadequate to conclude a causal relationship between "persistent" sexual dysfunction events and SSRI/ SNRI therapy.

3. Consultant's Conclusion

In men, SSRI/ SNRIs therapy affects:

- Ejaculation – the effect has been described as "ejaculatory delay" or as "ejaculatory failure",
- Libido – the effect has been described as "decreased libido", and
- Erectile function – though not as much as it affects ejaculation and libido - the effect has been described as "erectile dysfunction".

While SSRI/SNRI therapy might also affect orgasm in men, the evidence for orgasmic dysfunction in men is not extensive, and not nearly as compelling as the evidence for ejaculatory delay/ejaculatory failure and decreased libido. It remains unclear as to what specific clinical events are reflected in SSRI/SNRI labeling as male "anorgasmia" and "abnormal orgasm".

Some of these male "anorgasmia" and "abnormal orgasm" events probably reflect ejaculatory delay/ejaculatory failure and are not true male "anorgasmia" or 'abnormal orgasm" events. In addition, these types of events are reported at very low incidences and not in all trials of SSRIs/SNRIs.

Finally, while there are reports of sexual dysfunction events that arose in men while on SSRI/ SNRI therapy and persisted after discontinuation of SSRI/ SNRI therapy, and reports of sexual dysfunction events that arose in men after discontinuation of SSRI/ SNRI therapy and persisted; in most of these cases, multiple clinical confounders are present and clinical detail is lacking. No additional evidence is available from controlled clinical studies to better inform a causality determination for these types of events. Overall, the available evidence is inadequate to conclude a causal relationship between "persistent" sexual dysfunction events and SSRI/ SNRI therapy.

4. Consultant's Responses to the Consult Question

In this section, we provide a response to the following consult question posed by DPP:

Please assess the strength of available evidence that SSRIs and SNRIs cause any of the following adverse events (a) while on treatment and (b) following discontinuation of the SSRI/SNRI (discussing the duration of persistence if information is available). You may combine items in the list if you consider them to be describing the same clinical phenomena.

1. **Genital anesthesia**

   Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes genital anesthesia in men.

2. **Pleasureless or weak orgasm**

   Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes "pleasureless or weak orgasm" in men.

3. **Delayed or absent orgasm**

   Consultant's Response: The available evidence may weakly support that SSRI/ SNRI therapy affects orgasm in men. However, the evidence for SSRI/ SNRI-related orgasmic dysfunction in men is not extensive, and is not nearly as compelling as the evidence for SSRI/ SNRI-related ejaculatory delay/ejaculatory failure and decreased libido. It remains unclear as to what specific clinical events are reflected in SSRI/SNRI labeling as male "anorgasmia" and "abnormal orgasm". Some of these events probably reflect ejaculatory delay/ejaculatory failure and are not true male "anorgasmia" or "abnormal orgasm" events. In addition, these types of events are reported at very low incidences and do not occur in all trials of SSRIs/SNRIs, which speaks against a clear effect of SSRIs/ SNRIs on male orgasm.

4. **Loss of libido**

Consultant's Response: The available evidence supports that SSRI/ SNRI therapy affects male libido. The effect has been described as "decreased libido".

5. **Erectile dysfunction**

   Consultant's Response: The available evidence supports that SSRI/ SNRI therapy affects erectile function, but not as much as it affects male libido and ejaculation. The effect has been described as "erectile dysfunction".

6. **Reduced nipple sensitivity**

   Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes "reduced nipple sensitivity" in men.

   .

7. **Flaccid glans penis during erection (if this is distinct from erectile dysfunction?)**

   Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes "flaccid glans penis during erection" separate from its effect on male erectile function. See our response to Item 5 above.

8. **Reduced response to sexual stimuli**

   Consultant's Response: The available evidence does not support that SSRI/SNRI therapy causes "reduced response to sexual stimuli" separate from its effects on male libido, ejaculation, and erectile function. See our Conclusion and our responses to Items 3, 4 and 5 above.

9. **Decreased capacity to experience sexual pleasure**

   Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes "decreased capacity to experience sexual pleasure" in men separate from its effects on male libido, ejaculation, and erectile function. See our Conclusion and our responses to Items 3, 4 and 5 above.

10. **[if applicable]: Persistent genital arousal disorder (defined in petition as an uncontrollable and relentless feeling of physiological arousal in the genitals but without any accompanying feeling of sexual desire)**

    Consultant's Response: The available evidence does not support that SSRI/ SNRI therapy causes "persistent genital arousal disorder" in men.

Finally, while there are reports of sexual dysfunction events that arose in men while on SSRI/ SNRI therapy and persisted after discontinuation of SSRI/ SNRI therapy, and reports of sexual dysfunction events that arose in men after discontinuation of SSRI/ SNRI therapy and persisted; in most of these cases, multiple clinical confounders are present and clinical detail is lacking. No

additional evidence is available from controlled clinical studies to better inform a causality determination for these types of events. Overall, the available evidence is inadequate to conclude a causal relationship between "persistent" sexual dysfunction events and SSRI/ SNRI therapy.

APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

A R WIEDERHORN
06/09/2021 02:06:56 PM

MARK S HIRSCH
06/09/2021 03:29:37 PM
Note: Our Division (DUOG) was formerly known as the Division of Bone, Reproductive and Urologic Products (DBRUP).

CATHERINE A SEWELL
06/09/2021 05:01:27 PM

The Division of Urology, Obstetrics and Gynecology (DUOG)
Clinical Review

Application	Drug	Applicant	Indication
NDA 018936	Sarafem (fluoxetine) oral capsules	Eli Lilly and Company	Treatment of premenstrual dysphoric disorder
NDA 021860	Sarafem (fluoxetine) oral tablets	Allergan Pharmaceuticals International LTD	Treatment of premenstrual dysphoric disorder
NDA 204516	Brisdelle (paroxetine) oral capsules	Sebela Ireland Ltd. c/o Sebela Pharmaceuticals, Inc.	Treatment of vasomotor symptoms associated with menopause

From: Marcea Whitaker, M.D., Medical Officer, DUOG

Through: Christina Chang, M.D., M.P.H., Team Leader (Reproductive), DUOG

Subject: Safety Labeling Changes for Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)

1. Background:

On May 10, 2018, the Agency received a Citizen's Petition (CP, docket # FDA-2018-P-1846) from Data Based Medicine Americas, Ltd., requesting that FDA immediately revise all SSRI and SNRI labeling as follows:

- Add WARNINGS, PRECAUTIONS, and HIGHLIGHTS OF PRESCRIBING INFORMATION to inform that the use of, and withdrawal from, SSRIs and SNRIs can result in "genital anesthesia", "pleasureless or weak orgasm", "delayed or absent orgasm", "loss of libido", "erectile dysfunction", "decreased vaginal lubrication", "reduced nipple sensitivity", "flaccid glans penis during erection", "reduced response to sexual stimuli", "decreased capacity to experience sexual pleasure", and "persistent genital arousal disorder (PGAD)".

- Add WARNINGS, PRECAUTIONS, HIGHLIGHTS OF PRESCRIBING INFORMATION, and a BOXED WARNING to inform that sexual side effects can sometimes persist for years or indefinitely after discontinuation of the drug; that they can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.

The Petitioner also requests FDA to issue a notification letter requiring a REMS of all manufacturers of SSRIs and SNRIs. Specifically, the Petitioner requests that FDA require manufacturers to take the following actions:

- Send a Dear Health Care Provider letter to psychiatrists, psychologists, internists, family practitioners, urologists and endocrinologists informing them that these drugs have serious adverse reactions (as described above) and pose a significant public health concern; and
- Develop a Medication Guide and Communication Plan to make patients aware that the drugs have serious risks (as described above) that could affect the patient's decision to use or to continue to use the product.

The Petitioner states that current labeling does not adequately convey the breadth, severity or potentially permanent nature of the adverse sexual effects from SSRI and SNRI products. The Petitioner states that neither patients nor health care professionals can reasonably be expected to know the full impact of the products on sexual functioning that could include "profound genital numbness" and "the loss of ability to experience pleasure during orgasm", and therefore it is not possible for patients to weigh the benefits of treatment against the harms of SSRIs and SNRIs.

Currently, all SSRIs and SNRIs contain some language regarding adverse effects on sexual function. However, none of the SSRIs or SNRIs contain a Boxed Warning regarding adverse sexual effects.

2. DP's Conclusions and Recommendations

The Office of Regulatory Policy (ORP) consulted the Division of Psychiatry (DP) to address the issues raised by the Petitioner. On August 28, 2018, DP consulted DUOG to evaluate reports of sexual adverse effects in males and females receiving SSRIs and SNRIs. Draft reviews from both the repro team and the urology team were forwarded to DP on July 26, 2019 and July 13, 2019, respectively. The repro team's review was officially entered into DARRTS on June 8, 2021; the urology team's review was finalized in DARRTS on June 9, 2021.

In a March 26, 2021 meeting, DP informed DUOG that, after reviewing the input from DUOG and the Office of Surveillance and Epidemiology (Division of Pharmacovigilance I), they intended to issue safety labeling change notifications to all NDA and ANDA holders of SSRIs/SNRIs regarding the risks of sexual dysfunction. The agreed-upon language, shown in the Appendix, included a Warnings and Precaution for sexual dysfunction regarding ejaculatory delay or failure, decreased libido, and erectile dysfunction in males and decreased libido and delayed or absent orgasm in females; update to section 17 Patient Counseling Information; and the addition to the Medication Guide.

DP and the Office of Regulatory Policy (ORP) continue to review the Agency's response to the CP. ORP will issue a response in full to the petitioner when their review for the CP is complete.

Under DUOG's jurisdiction, there are two selective serotonin reuptake inhibitors (SSRI) approved for indications: fluoxetine, approved as Sarafem capsules and tablets (under separate NDAs), for the treatment of premenstrual dysphoric disorder, and paroxetine, approved as Brisdelle tablets, for the treatment of vasomotor symptoms associated with menopause. In the current Sarafem product labeling, mentions of female sexual dysfunction is limited to the Adverse Event, Clinical Trials Experience section. In the current Brisdelle labeling, there is no mention of sexual dysfunction.

In coordination with DP's decision to issue SLC notifications, DUOG will also issue SLC notifications to holders of the Sarafem and Brisdelle NDAs on the same day. The language included in these SLC notifications for these products is specific to the female population because these products are not indicated for use in males.

3. Appendix

Class Labeling for SSRI/SNRIs

Highlights

----------**WARNINGS AND PRECAUTIONS** ----------

- Sexual Dysfunction: DRUG X use may cause symptoms of sexual dysfunction (5.X)

5 WARNINGS AND PRECAUTIONS

5.X Sexual Dysfunction

Use of SSRIs, including DRUG X, may cause symptoms of sexual dysfunction *[see Adverse Reactions (6.X)]*. In male patients, SSRI use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, SSRI use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Drug X and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Sexual Dysfunction

Advise patients that use of DRUG X may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings* and *Precautions (5.X)].*

MEDICATION GUIDE

- **Sexual problems (dysfunction).** Taking selective serotonin reuptake inhibitors (SSRIs), including DRUG X, may cause sexual problems.

  Symptoms in males may include:
  - Delayed ejaculation or inability to have an ejaculation
  - Decreased sex drive
  - Problems getting or keeping an erection

  Symptoms in females may include:
  - Decreased sex drive
  - Delayed orgasm or inability to have an orgasm

  Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with DRUG X. There may be treatments your healthcare provider can suggest.

Additionally, DP is requesting that all Applicants update the OVERDOSE section of product labeling and add the information below:

10 OVERDOSAGE

The following have been reported with fluoxetine tablet overdosage:

- Seizures, which may be delayed, and altered mental status including coma.
- Cardiovascular toxicity, which may be delayed, including QRS and QTc interval prolongation, wide complex tachyarrhythmias, torsade de pointes, and cardiac arrest. Hypertension most commonly seen, but rarely can see hypotension alone or with co-ingestants including alcohol.
- Serotonin syndrome (patients with a multiple drug overdosage with other pro- serotonergic drugs may have a higher risk).

Gastrointestinal decontamination with activated charcoal should be considered in patients who present early after a fluoxetine overdose.

Consider contacting a Poison Center (1-800-221-2222) or a medical toxicologist for additional overdosage management recommendations.

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/s/

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06/15/2021 05:13:31 PM

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06/15/2021 05:14:55 PM

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06/15/2021 05:19:52 PM

Consultative Review

To:	Division of Psychiatric Products (DPP)
From:	Marcea Whitaker, M.D., Medical Officer, DBRUP
Through:	Christina Chang, M.D., M.P.H., Team Leader, DBRUP Christine Nguyen, M.D., Deputy Director for Safety, DBRUP
Date received:	May 10, 2018
Date completed:	July 26, 2019
Drug Classes:	selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs)
Re:	Citizen's Petition (docket no. FDA-2018-P-1846) adverse effects of SSRIs/SNRIs (multiple NDAs) on female sexual function

1. INTRODUCTION

This consult review documents the DBRUP repro team's response to DPP's request to assist in DPP's review of a Citizen's Petition (CP) submitted on May 10, 2018, by Data Based Medicine Americas Ltd. (hereafter referred to as the Petitioner). The CP requests that FDA revise the SSRI/SNRI labels as follows:

1. Add Warnings, Precautions, and HIGHLIGHTS OF PRESCIRBING INFORMATION to inform that the use of and withdrawal from SSRIs and SNRIs can result in a wide array of sexual dysfunction side effects;
2. Add Warnings, Precautions, and HIGHLIGHTS OF PRESCIRBING INFORMATION to inform that the use of and withdrawal from SSRIs and SNRIs can result in persistent genital arousal disorder (PGAD)
3. Add Warnings, Precautions, and HIGHLIGHTS OF PRESCIRBING INFORMATION, and a BOXED WARNING (BW) to inform sexual side effects can sometimes persist for years or indefinitely after drug discontinuation.

The Petitioner also requests that FDA issue a notification letter to all SSRI/SNRI manufacturers to require a Risk Evaluation and Mitigation Strategy Plan be implemented.

This review focuses on SSRI/SNRI's impact on women's sexual function; a separate DBRUP urology consult review addresses the drugs' adverse sexual effects in men.

DPP specifically requests DBRUP repro team to:

1. Assess the strength of available evidence that SSRIs and SNRIs cause any of the following adverse events in women 1) while on treatment and 2) following discontinuation of the drug:
    a. Genital anesthesia

b. Pleasureless or weak orgasm
c. Delayed or absent orgasm
d. Loss of libido
e. Reduced nipple sensitivity
f. Vaginal dryness
g. Reduced response to sexual stimuli
h. Decreased capacity to experience sexual pleasure
i. Persistent general arousal disorder (defined in petition as an uncontrollable and relentless feeling of physiological arousal in the genitals but without any accompanying feeling of sexual desire)

Of note, the Petitioner submitted an identical petition to the European Medicines Agency (EMA). The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) recently recommended the following changes be made: [1]

- Summary of product characteristics, Section 4.4 Special Warnings and precautions for use, to add the text in italic font below:
  - *Sexual dysfunction*
    Selective serotonin reuptake inhibitors (SSRIs)/serotonin norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction (see section 4.8). There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRI.
- Package leaflet, Section 2 What you need to know before you take [insert name], to add the text in italic font below:
  - Warnings and precautions
    Medicines like [insert name] (so called SSRIs/SNRIs) may cause symptoms of sexual dysfunction (see section 4). In some cases, these symptoms have continued after stopping treatment.

2. BACKGROUND

The term "female sexual dysfunction" encompasses a heterogeneous group of sexual disorders, such as dyspareunia and problems related to sexual arousal, desire, interest, or orgasm. The sexual response in women has a physiological basis but can be affected by interpersonal context, such as emotional and relationship dynamics. Significant changes in any of these components can affect a woman's sexual desire, response, and satisfaction. A variety of factors can cause or contribute to sexual dysfunction, including medical conditions (such as symptoms of vulvovaginal atrophy related to menopause), psychiatric conditions (such as depression and anxiety), use of medications, and stressors (such as fatigue or relationship difficulties). Sexual dysfunction can adversely affect various aspects of life for a woman, including her relationship with her partner.[2]

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[1] Pharmacovigilance Risk Assessment Committee (PRAC) Recommendations on signals. Accessed July 8, 2019 at https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-13-16-may-2019-prac-meeting_en.pdf

[2] Low Sexual Interest, Desire, and/or Arousal in Women: Developing Drugs for Treatment. Draft Guidance for Industry. https://www.fda.gov/media/100833/download

There are a number of SSRIs/SNRIs that have been FDA-approved for mood or anxiety disorders. The complete list is included in Appendix 1. The FDA has acknowledged sexual dysfunction associated with antidepressants as an important entity that should be adequately assessed during clinical trials.[3] Approved labeling for each product generally includes information regarding adverse sexual function in Section 6 Adverse Reactions (i.e., decreased libido and anorgasmia). However, specific adverse reactions listed vary from product to product and may not make distinction between dysfunction in women vs. men, the type of sexual dysfunction as designated in the Diagnostic and Statistical Manual of Mental Disorders (DSM)[4] (e.g., desire, arousal, or orgasmic, etc.), or describe timing relative to treatment. No SSRI/SNRI labeling currently includes adverse sexual function in Section 5 Warnings and Precautions and none contains a BW or has a REMS to mitigate events of adverse sexual function.

3. REVIEW OF EVIDENCE

3.1 SSRI Product Labeling

With the exception of vortioxetine (Trintellix), the labeling of approved SSRIs includes the following template language (italic added).

> ***Male and female sexual dysfunction with SSRIs:***
> *Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.*
>
> *Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.*

As shown in Table 1, excluding vortioxetine, all SSRI labeling lists "libido decreased" as an adverse effect in placebo-controlled clinical trials. All but one (sertraline) also lists orgasmic dysfunction (anorgasmia or difficulty achieving orgasm) as an adverse effect in placebo-controlled clinical trials. Where incidences in placebo-controlled clinical trials for these two reactions were available for females, they are shown in Table 1 as well.

Notably, only fluoxetine labeling (added in 2011) states that symptoms of sexual dysfunction "occasionally persist after discontinuation of treatment." No other labeling mentions any symptoms persisting beyond SSRI discontinuation.

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[3] Khin NA, Kronstein PD, Yang P. Regulatory and scientific issues in studies to evaluate sexual dysfunction in antidepressant drug trials. J Clin Psychiatry. 2015;76(8);1060-1063.

[4] DSM 5 (2013, American Psychiatric Association) includes the following diagnoses under "Sexual Dysfunction" – female orgasmic disorder, female sexual interest/arousal disorder, genito-pelvic pain/penetration disorder, substance/medication-induced sexual dysfunction, other specified sexual dysfunction, and unspecified sexual dysfunction (only the diagnoses affecting women are listed). DSM IV Text Revision (2000) includes the following diagnoses under "Sexual and Gender Identity Disorders" – sexual desire disorders, sexual arousal disorders, orgasmic disorders, sexual pain disorders, sexual dysfunction due to a general medical condition, substance-induced sexual dysfunction.

Table 1: Adverse reactions consistent with female sexual dysfunction and incidences (if available) in SSRI labels

	Reaction	
Product	**Libido decreased**	**Orgasmic dysfunction**
Prozac/fluoxetine[5]	X (4% vs. <1% in placebo)	X (anorgasmia)
Paxil/paroxetine[6]	X (0-9% vs. 0-2% in placebo)	X (anorgasmia, difficulty achieving orgasm or delayed orgasm) (2-9% vs. 0-1% in placebo)
Zoloft/sertraline[7]	X (4% vs. 2% in placebo)	
Luvox/fluvoxamine[8]	X (2% vs. 1% in placebo)	X (anorgasmia) (2% vs. 0% in placebo)
Celexa/citalopram[9]	X (1.3%)	X (anorgasmia) (1.1%)
Lexapro/escitalopram[10]	X (3% vs. 1% in placebo)	X (anorgasmia) (3% vs. <1% in placebo)
Viibryd/vilazodone[11]	X	X (abnormal orgasm and anorgasmia)
Trintellix/vortioxetine[12]	Unspecified treatment emergent sexual dysfunction 20% - 34% depending on daily dose	

In vortioxetine labeling, development of sexual dysfunction while on treatment was described in more detail than in other SSRI labeling. "Treatment-emergent sexual dysfunction" (TESD) overall is said to be reduced relative to other SSRIs in clinical trials. In seven placebo-controlled trials in the vortioxetine program, the Arizona Sexual experiences Scale (ASEX) was used to prospectively assess the development of TESD in patients with normal sexual functioning at baseline. Compared to female patients on placebo, in whom 20% developed TESD, dose-dependent incidences of TESD were seen in female patients on vortioxetine (22% on 5 mg/day, 23% on 10 mg/day, 33% on 15 mg/day, and 34% on 20 mg/day). Vortioxetine was also prospectively compared to escitalopram and paroxetine, using the total score from a patient-reported outcome instrument – Changes in Sexual Functioning Questionnaire Short Form (CSFQ-14). However, the types of sexual dysfunction(s) mitigated with vortioxetine were not specified.

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[5] Prozac package insert approved on March 24, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/018936s103,021235s023lbl.pdf
[6] Paxil package insert approved on January 4, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020936s053lbl.pdf
[7] Zoloft package insert approved on December 8, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/019839s091lbl.pdf
[8] Luvox package insert approved on April 14, 2008, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2008/022235lbl.pdf
[9] Celexa package insert approved on January 11, 2019, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/020822s051lbl.pdf
[10] Lexapro package insert approved on January 11, 2019, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/021323s051,021365s036lbl.pdf
[11] Viibryd package insert approved on January 4, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022567s020lbl.pdf
[12] Trintellix package insert approved on October 19, 2018 https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/204447s017lbl.pdf

3.2 SNRI Product Labeling

SNRI products do not have the same template language describing the potential for developing treatment-emergent sexual dysfunction as in SSRI product labeling. Among SNRI product labeling, duloxetine labeling includes the most detail related to adverse sexual functioning. Similar to the clinical development for vortioxetine, ASEX was also to prospectively assess TESD in four placebo-controlled duloxetine trials. Contrary to the findings in males, females did not experience more sexual dysfunction on duloxetine than on placebo as measured by overall ASEX score or for any subtype of sexual function assessed (sex drive, arousal, lubrication, ease of reaching orgasm, orgasm satisfaction). Reactions that are captured in SNRI product labeling are shown in Table 2.

Table 2: Adverse reactions consistent with female sexual dysfunction and incidences (if available) in SNRI labels

	Reaction	
Product	**Libido decreased**	**Orgasmic dysfunction**
Effexor/venlafaxine[13]	X (did not specify gender)	X (anorgasmia)
Cymbalta/duloxetine[14]	X (also includes loss of libido)	X (orgasm abnormal, including anorgasmia) (2% vs. 0.2% in placebo)
Pristiq/desvenlafaxine[15]		X (anorgasmia)
Savella/milnacipran[16]*		
Fetzima/levomilnacipran*[17]		

* Labeling includes only adverse reactions in men.

3.3 Literature

We have reviewed the literature references submitted by the Petitioner, consisting primarily of review articles, case series/reports and primarily documented sexual dysfunction in men.

3.3.1 Treatment-emergent sexual dysfunction

Sexual dysfunction, characterized by disturbances in the sexual response cycle, is common in the general population in the United States. In US women, sexual dysfunction is prevalent (estimated to affect 43% of US women)[18] and distressing to women (22% reporting personal distress over the dysfunction).[19] In women, reduced sexual desire appears to be the most common form (age-adjusted rate of 38%), followed by low arousal (25%) and low orgasm (21%).[19] However, because the background rates of sexual dysfunction in patients with mood and anxiety disorders are also high, it is challenging to assess the degree of sexual dysfunction over baseline that is

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[13] Effexor XR package insert approved on December 19, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/020699s110s111lbl.pdf

[14] Cymbalta package insert approved on December 19, 2017, at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021427

[15] Pristiq package insert approved on February 6, 2018, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021992s042lbl.pdf

[16] Savella package insert approved on December 19, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/022256s023lbl.pdf

[17] Fetzima package insert approved on December 19, 2017, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204168s005lbl.pdf

[18] Laumann EO, Paik A, Rosen RC. Sexual dysfunction in the United States: prevalence and predictors. JAMA. 1999;281:537-544.

[19] Shifren JL, Monz BU, Russo PA, Segreti A, Johannes CB. Sexual problems and distress in the United States women. Obstet Gynecol. 2008;112(5):970-978.

directly attributed to therapy with SSRIs/SNRIs. As reported by Montejo et al, in patients with previously normal sexual function and began treatment with various SSRIs and venlafaxine, the incidence of sexual dysfunction ranged from 58% with fluoxetine to 73% with citalopram.[20] The clinical programs for vortioxetine and duloxetine also made efforts in characterizing the extent of TESD with treatment. As indicated in current approved SSRI/SNRI product labeling, the FDA already recognizes TESD as an important clinical entity.

3.3.2 Persistence of sexual dysfunction post treatment

Cases of post-SSRI sexual dysfunction ("PSSD") in the references submitted by the Petitioner are summarized in Table 3.

Table 3. PSDD cases in women in the literature

Study	N	Age (yr)	Symptoms	SSRI Treatment
Csoka[21]	1	27	Loss of libido, reduction in genital and nipple sensitivity and anorgasmia	fluoxetine
Kauffman[22]	1	32	Genital anesthesia, orgasmic disorder	citalopram
Lareb Quarterly report[23]*	6	20 to 59	Loss of libido, orgasmic disorder	paroxetine, sertraline, venlafaxine, citalopram, fluoxetine
Stinson[24]	5	25 to 34	Loss of libido, orgasmic disorder, genital anesthesia	citalopram, escitalopram, fluoxetine, paroxetine, sertraline
Hogan[25]	15	15 to 65	Loss of libido, genital anesthesia, orgasm difficulty, vaginal dryness/pain	Multiple SSRIs, individual treatment information not available
Ben-Sheetrit[26]	4	25 to 26	Genital anesthesia, "pleasureless orgasm"	Fluoxetine, citalopram,
Healy	49	15 to 54	Loss of libido, genital anesthesia, difficulty achieving orgasm, "pleasureless or weak orgasm," vaginal dryness/pain, reduced nipple sensitivity, persistent genital arousal disorder	Escitalopram, citalopram, sertraline, fluoxetine, venlafaxine, duloxetine

*Some information extracted from Reisman et al.[27]

[20] Montejo AL, Llorca G, Izquierdo JA, Rico-Villademoros F, for the Spanish Working group for the Study of Psychotropic-Related Sexual Dysfunction. Incidence of sexual dysfunction associated with antidepressant agents: a prospective multicenter study of 1022 outpatients. J Clin Psychiatry. 2001;62(suppl 3):10-21.
[21] Csoka AB, Shipko S. Persistent sexual side effects after SSRI discontinuation. Psychother Psychosom. 2006;75(3):187-8.
[22] Kauffman RP, Murdock A. Prolonged post-treatment genital anesthesia and sexual dysfunction following discontinuation of citalopram and the atypical antidepressant nefazodone. The Open Women' Health Journal 2007;1:1-3.
[23] SSRIs and persistent sexual dysfunction. Lareb quarterly report. Dutch Pharmacovigilance Center. (This review team is not able to access the report from the link provided by the Petitioner, http://databankws.lareb.nl/Downloads/KWB_2012_3_SSRI.pdf)
[24] Stinson RD. The impact of persistent sexual side effects of selective serotonin reuptake inhibitors after discontinuing treatment: a qualitative study. PhD (Doctor of Philosophy) thesis, University of Iowa 2013. At https://ir.uiowa.edu/cgi/viewcontent.cgi?referer=&httpsredir=1&article=5061&context=etd. Accessed July 21, 2019.
[25] Hogan C, Noury JL, Healy D, Mangin D. One hundred and twenty cases of enduring sexual dysfunction following treatment. Int J Risk Saf Med. 2014;26:109-116.
[26]Ben-Sheetrit J, Aizenberg D, Csoka AB, Weizman A, Hermesh H. Post-SSRI sexual dysfunction: clinical characterization and preliminary assessment of contributory factors and dose-response relationship. J Clin Psychopharmacol. 2015;35:273-278.
[27] Reisman Y. Sexual Consequences of Post-SSRI Syndrome. Sex Med Rev. 2017;5(4):429-433.

It should be noted that cases reported by Hogan, Ben-Sheetrit, and Healy were all collected by an Internet-based forum dedicated to PSSD (SSRIsex – Persistent SSRI Sexual Side Effects, affiliated with the Petitioner. It is not clear whether duplicated cases were cited in these publications. Further, we have not identified any controlled clinical trials to address the question of whether sexual dysfunction persists following the discontinuation of SSRI/SNRI treatment in women. Absent controlled clinical trials, it is challenging to attribute drug causality based on uncontrolled studies or case reports.

3.3.3 Persistent genital arousal disorder

The strength of evidence regarding "Persistent Genital Arousal Disorder (PGAD)" is even weaker. Cases classified as PGAD often include significant confounding information, such as personal history of depression/anxiety or sexual abuse, rendering a determination of causal relationship with SSRI/SNRI treatment virtually impossible.

We note that PGAD is not a recognized medical condition in either DSM or the International Statistical Classification of Diseases and Related Health Problems (ICD, currently the 10th revision). In fact, at the 2017 International Consultation on Sexual Medicine, a Committee that evaluated female sexual dysfunction concluded the following regarding PGAD (italic added):

> *"Although recognized as a serious condition, PGAD still lacks an empirically supported framework…PGAD is a serious condition affecting women's emotional well-being. No [randomized controlled trial] has been conducted on any of the potential treatments. There is only anecdotal evidence indicating that a set of organic and pharmacologic conditions might underpin PGAD."*[28]

3.4 Postmarketing Data

Review of the cases identified by the Office of Surveillance and Epidemiology as PGAD are shown below. No determination of causality can be made due to significant confounding by the patients' psychiatric disease and very limited information available.

No	Case	age	Associated drug	Description
1	11887761	57 F	Citalopram 20 mg	PGAD following citalopram withdrawal; assessment confounded by hospitalization for suicidal ideation
2	136665700	45 F	Citalopram 20, 30 mg	PGAD with increased dose, resolved after dose decreased
3	6755323	52 F	Effexor	PGAD after stopping venlafaxine (unclear whether treatment duration was 6 yrs or 6months)
4	6755360	37 F	Effexor (venlafaxine) Literature	PGAD while on therapy and after treatment
5	6809213	52 F	Citalopram Literature	PGAD on treatment
6	7328125	--	Paroxetine literature	Long history of PGAD after abrupt discontinuation of Paxil

[28] Kingsberg SA, Althof S, Simon J, Bradford A, Bitzer J, Carvalho J, Flynn K, Nappi R, Reese J, Rezaee R, Schover L, Shifrin JL. Female Sexual Dysfunction – Medical and Psychological Treatments, Committee 14. International Consultation on Sexual Medicine Report. J Sex Med. 2017;14:1463-1491.

7	9203487	60 F	Fluoxetine Sertraline Venlafaxine escitalopram	PGAD after fluoxetine, recurred with other SSRIs
8	9656650	--	escitalopram	PGAD 5 days after starting medication, symptoms stopped after discontinuing medication

We defer to the Division of Pharmacovigilance I for their comprehensive review of postmarketing information.

4. CONCLUSIONS AND RECOMMENDATIONS

1. The emergence of sexual dysfunction during treatment with SSRI/SNRI is well recognized clinically and well documented. Wherever data are available, current product labeling includes some description of treatment-emergent sexual dysfunction. Although the overall incidence of treatment-emergent sexual dysfunction in women appears to be low, because disturbance of sexual function can significantly affect how patients feel and function, some patients may determine that the adverse effect of SSRI/SNRI therapy outweighs the benefit. Viewed in this light, elevating treatment-emergent sexual dysfunction to a warning (and included in Section 5 Warnings and Precautions of labeling) appears reasonable to ensure that patients are fully informed when starting therapy.
    a. Corresponding information would be appropriate in Section 17 Patient Counseling Information.
    b. With the addition of sexual adverse events to Warnings and Precautions, a Medication Guide may be reasonable since the events reflect a serious risk that could affect a patient's decision to use or continue use of the drug (21 CFR 208.1).
    c. Decreased libido (sexual desire) in women was noted universally with SSRIs in two SRNIs; available evidence does support the inclusion in Section 5 of product labeling.
    d. Various terms have been used to describe "abnormal orgasm," including anorgasmia, difficulty achieving orgasm, delayed orgasm, etc. But collectively, orgasmic difficulty is included in all but one SSRI product labeling (i.e., sertraline). Again, available evidence supports inclusion in Section 5 of labeling.

2. There are no controlled clinical trial data to suggest that symptoms of sexual dysfunction that persists following discontinuation of SSRI/SNRI treatment are causally associated with SSRI/SNRI. Reports of reduced sexual function post-SSRI/SNRI are primarily based on patient recollection and may be subject to recall bias at the time of the clinic visits when this information is collected. Based on case reports in literature, which typically contain limited clinical information, we are unable to determine whether the patients' underlying mood/anxiety disorder is adequately controlled off SSRI/SNRI treatment (a significant confounder). At most, addition of individual adverse reactions (e.g., decreased libido) based on available reports rather than the nonspecific term "sexual dysfunction" after SSRI/SNRI treatment could be considered for Section 6 Adverse Reactions (in postmarketing experience) of labeling. We do not support

describing persistent sexual dysfunction after treatment discontinuation in Section 5 Warnings and Precautions.

3. Available evidence does not support considering persistent genital arousal disorder (PGAD) as a clinical entity. We do not believe that inclusion of cases identified as PGAD in any section of product labeling is warranted.

4. Reactions such as genital anesthesia, reduced nipple sensitivity, reduced response to sexual stimuli, and "pleasureless or weak orgasm" are vague and nonspecific, although the first three reactions might be related to reduced sexual arousal. At this time, we do not recommend including these terms in labeling.

5. APPENDIX

Appendix 1. Approved SSRIs/SNRIs by NDA #s

Application Number	Brand/Proprietary Name	Chemical/Generic Name	Established Pharmacologic Class (EPC)
NDA 018207	DESYREL®	TRAZODONE HYDROCHLORIDE	SSRI
NDA 018936	PROZAC®	FLUOXETINE HYDROCHLORIDE	SSRI
NDA 019839	ZOLOFT®	SERTRALINE HYDROCHLORIDE	SSRI
NDA 020031	PAXIL®	PAROXETINE HYDROCHLORIDE	SSRI
NDA 020710	PAXIL®	PAROXETINE HYDROCHLORIDE	SSRI
NDA 020699	EFFEXOR® XR	VENLAFAXINE HYDROCHLORIDE	SNRI
NDA 020822	CELEXA®	CITALOPRAM HYDROBROMIDE	SSRI
NDA 020885 DISCONTINUED	PAXIL®	PAROXETINE HYDROCHLORIDE	SSRI
NDA 020936	PAXIL® CR	PAROXETINE HYDROCHLORIDE	SSRI
NDA 020990	ZOLOFT®	SERTRALINE HYDROCHLORIDE	SSRI
NDA 021235	PROZAC® WEEKLY	FLUOXETINE HYDROCHLORIDE	SSRI
NDA 021323	LEXAPRO®	ESCITALOPRAM OXALATE	SSRI
NDA 021440	LEXAPRO®	ESCITALOPRAM OXALATE	SSRI
NDA 021365	LEXAPRO®	ESCITALOPRAM OXALATE	SSRI
NDA 021299	PEXEVA®	PAROXETINE MESYLATE	SSRI
NDA 021427	CYMBALTA®	DULOXETINE HYDROCHLORIDE	SNRI
NDA 021992	PRISTIQ®	DESVENLAFAXINE	SNRI
NDA 022104	VENLAFAXINE ER	VENLAFAXINE HYDROCHLORIDE	SNRI
NDA 022411	OLEPTRO®	TRAZODONE HYDROCHLORIDE	SSRI
NDA 022567	VIIBRYD®	VILAZODONE HYDROCHLORIDE	SSRI
NDA 202133	FLUOXETINE	FLUOXETINE HYDROCHLORIDE	SSRI
NDA 204150	DESVENLAFAXINE ER	DESVENLAFAXINE	SNRI
NDA 204683	KHEDEZLA™	DESVENLAFAXINE	SNRI
NDA 204168	FETZIMA®	LEVOMILNACIPRAN	SNRI
NDA 204447	TRINTELLIX™	VORTIOXETINE HYDROBROMIDE	SSRI
NDA 205583	APTRYXOL™	DESVENLAFAXINE FUMARATE	SNRI
NDA 022033	LUVOX CR®	FLUVOXAMINE MALEATE	SSRI
NDA 022235	LUVOX	FLUVOXAMINE MALEATE	SSRI
NDA 020982	PAXIL® CR	PAROXETINE HYDROCHLORIDE	SSRI
NDA 021411	STRATTERA®	ATOMOXETINE HYDROCHLORIDE	SNRI

Source: DPP consult request dated May 28, 2018

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/s/

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06/08/2021 04:41:47 PM

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06/08/2021 04:43:40 PM

FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

Date: May 28, 2021

To: Office of Regulatory Policy citizen petition file for docket no. FDA-2018-P-1846

From: Marc Stone, MD
Deputy Director for Safety, Division of Psychiatry

Through: Tiffany Farchione, MD
Director, Division of Psychiatry

Subject: Safety labeling changes for selective serotonin reuptake inhibitor (SSRI) and serotonin-norepinephrine reuptake inhibitor (SNRI) drug products and pending citizen petition FDA-2018-P-1846

This memorandum addresses issues raised in pending citizen petition FDA-2018-P-1846 (the Petition) that relate to new safety information that the Food and Drug Administration (FDA or the Agency) has determined should be included in the labeling for all SSRI and SNRI drug products.

Background

A citizen petition submitted on behalf of Data Based Medicine Americas Ltd. was received by FDA on May 10, 2018. The Petition requests, among other things, that FDA:

- Add WARNINGS, PRECAUTIONS, and HIGHLIGHTS OF PRESCRIBING INFORMATION to inform that the use of and withdrawal from SSRIs and SNRIs can result in genital anesthesia, pleasureless or weak orgasm, delayed or absent orgasm, loss of libido, erectile dysfunction, decreased vaginal lubrication, reduced nipple sensitivity, flaccid glans penis during erection, reduced response to sexual stimuli, decreased capacity to experience sexual pleasure, and persistent genital arousal disorder.
- Add WARNINGS, PRECAUTIONS, HIGHLIGHTS OF PRESCRIBING INFORMATION, and a BOXED WARNING to inform that sexual side effects can sometimes persist for years or indefinitely after discontinuation of the drug; they can emerge on treatment and remain afterwards, or emerge or worsen when the drug is stopped.

Although this Petition continues to be under review by FDA, the Division of Psychiatry (DP) has become aware of new safety information that it has determined should be included in the labeling of all SSRI and SNRI drug products. Accordingly, DP is notifying the appropriate application holders of the new safety information that should be included in SSRI and SNRI product labeling in accordance with section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act. The proposed safety labeling changes (SLCs) would revise the labeling for all SSRI and SNRI products as follows:

1. Add to the end of WARNINGS AND PRECAUTIONS in the Highlights of Prescribing Information
    - Sexual Dysfunction: DRUG X may cause symptoms of sexual dysfunction. (5.X)

2. Add to the end of the WARNINGS AND PRECAUTIONS section of labeling

5.X Sexual Dysfunction
Use of [*SSRIs or SNRIs, as appropriate*], including DRUG X, may cause symptoms of sexual dysfunction [*include cross-reference to 6.1, if appropriate*]. In male patients, [*SSRI or SNRI*] use may result in ejaculatory delay or failure, decreased libido, and erectile dysfunction. In female patients, [*SSRI or SNRI*] use may result in decreased libido and delayed or absent orgasm.

It is important for prescribers to inquire about sexual function prior to initiation of Drug X and to inquire specifically about changes in sexual function during treatment, because sexual function may not be spontaneously reported. When evaluating changes in sexual function, obtaining a detailed history (including timing of symptom onset) is important because sexual symptoms may have other causes, including the underlying psychiatric disorder. Discuss potential management strategies to support patients in making informed decisions about treatment.

3. Add to the PATIENT COUNSELING INFORMATION section of labeling

Advise the patient to read the FDA-approved patient labeling (Medication Guide). [*Under the section title*]

Sexual Dysfunction
Advise patients that use of DRUG X may cause symptoms of sexual dysfunction in both male and female patients. Inform patients that they should discuss any changes in sexual function and potential management strategies with their healthcare provider *[see Warnings and Precautions (5.X)]*.

4. Add to the Medication Guide

Sexual problems (dysfunction). Taking [*serotonin reuptake inhibitors (SSRIs) or serotonin and norepinephrine reuptake inhibitors (SNRIs), as appropriate*], including DRUG X, may cause sexual problems.

Symptoms in males may include:
- Delayed ejaculation or inability to have an ejaculation
- Decreased sex drive
- Problems getting or keeping an erection

Symptoms in females may include:
- Decreased sex drive
- Delayed orgasm or inability to have an orgasm

Talk to your healthcare provider if you develop any changes in your sexual function or if you have any questions or concerns about sexual problems during treatment with DRUG X. There may be treatments your healthcare provider can suggest.

Discussion

DP is issuing SLC notification letters to the appropriate application holders for SSRI and SNRI drug products that describe the new safety information that DP has determined should be included in SSRI and SNRI product labeling. The SLCs would create a new warning about the risk of sexual dysfunction based on a review of new

safety information demonstrating that this risk is more clinically consequential than had been previously described in labeling, with corresponding additions also proposed for the Patient Counseling Information section. The proposed revisions to the Medication Guide are consistent with the proposed revisions to the prescribing information.

This SLC action would partially address the labeling changes requested in the Petition related to adding a new warning about the risk of sexual dysfunction, but would not address other requests such as including a listing of specific adverse reactions or information on the risks of persistent sexual dysfunction. While the decision to issue these SLC notification letters may be viewed as a partial grant of the Petition, it should not be construed as a partial denial because the Petition is still under review. FDA is still considering all requests in the Petition and will respond in full to the petitioner once our review is complete.

The SLC notification letters do not represent a final decision by the Agency on the merits of the pending citizen petition. Rather, the SLC notification letter reflects DP's determination that new safety information about the risks of sexual dysfunction with SSRI and SNRI drug products should be included in the product labeling.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: May 11, 2021

To: Kimberly Updegraff, PharmD, MS, Associate Director for Labeling, Division of Psychiatry (DP)

Ermias Zerislassie, PharmD, Safety Regulatory Project Manager, (DP)

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for:

PRISTIQ (desvenlafaxine) NDA-021992; KHEDEZLA (desvenlafaxine) NDA-204683; desvenlafaxine NDA-204150; desvenlafaxine fumarate NDA-205208; FETZIMA (levomilnacipran) NDA-204168; CYMBALTA (duloxetine delayed-release capsules) NDA-021427; EFFEXOR XR (venlafaxine Extended-Release) NDA-020699; venlafaxine hydrochloride NDA-022104; DRIZALMA SPRINKLE (duloxetine delayed-release capsules) NDA-212516; PROZAC WEEKLY (fluoxetine hydrochloride) NDA-021235; PROZAC (fluoxetine capsules) NDA-018936; fluoxetine NDA-202133; PAXIL (paroxetine) NDA-020885; PAXIL (paroxetine) NDA-020031; PAXIL (paroxetine) NDA-020710; PAXIL CR (paroxetine) NDA-020936; PEXEVA (paroxetine mesylate) NDA-021299; ZOLOFT (sertraline hydrochloride) NDA-019839; ZOLOFT (sertraline hydrochloride) NDA-020990; citalopram hydrobromide NDA-021763; CELEXA (citalopram hydrobromide) NDA-021046; CELEXA (citalopram hydrobromide) NDA-020822; LEXAPRO (escitalopram oxalate) NDA-021365; LEXAPRO (escitalopram oxalate) NDA-021323; VIIBRYD (vilazodone hydrochloride) NDA-022567; TRINTELLIX (vortioxetine) NDA-204447; SARAFEM (fluoxetine hydrochloride) NDA-021860

In response to the DP consult request dated May 10, 2021, OPDP has completed a focused review on the attached document for proposed labeling that provides for a Safety Labeling Change, received by DP (Kimberly Updegraff) on May 7, 2021. OPDP comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed Medication Guide were sent under separate cover on May 11, 2021.

Thank you for your consult. If you have any questions, please contact Dhara Shah at (240) 402-2859 or dhara.shah@fda.hhs.gov.

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/s/

DHARA SHAH
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date: May 11, 2021

To: Kimberly Updegraff, PharmD
Associate Director of Labeling (ADL)
Division of Psychiatry (DP)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Shawna Hutchins, MPH, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Dhara Shah, PharmD, RAC
Regulatory Review Ofiicer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guides (MGs) Safety Labeling Change Proposed Language

Drug Name (established name)	**Application Type/Number**	**Dosage Form And Route**	**Applicant**
PRISTIQ (desvenlafaxine)	NDA-021992	Tablets, for Oral use	PV Prism CV
KHEDEZLA (desvenlafaxine)	NDA-204683	Tablets, for Oral use	Osmotica Pharmaceuticals
desvenlafaxine	NDA-204150	Tablets, for Oral use	Alembic Pharmaceuticals, LTI
desvenlafaxine fumarate	NDA-205208	Tablets, for Oral use	Teva Pharmaceuticals USA, Inc
FETZIMA (levomilnacipran)	NDA-204168	Capsule, for Oral use	Allergan Sales, LLC
CYMBALTA	NDA-021427	For oral use	Eli Lilly and

(duloxetine delayed-Release capsules)			Company
EFFEXOR XR (venlafaxine Extended-Release)	NDA-020699	Capsules, for Oral use	Pfizer
venlafaxine hydrochloride	NDA-022104	Tablet, for Oral use	Osmotica Pharmaceuticals Corp
DRIZALMA SPRINKLE (duloxetine delayed-releas capsules)	NDA-212516	For oral use	Sun Pharmaceutical Industries
PROZAC WEEKLY (fluoxetine hydrochloride)	NDA-021235	Capsule, for Oral use	Eli Lilly and Co
PROZAC (fluoxetine capsules)	NDA-018936	For oral use	Lilly USA, LLC
fluoxetine	NDA-202133	Tablet, for Oral use	Alvogen Group Holdings 3, LLC
PAXIL (paroxetine)	NDA-020885	Capsule, for Oral use	Apotex Technologies, Inc.
PAXIL (paroxetine)	NDA-020031	Tablet, for Oral use	Apotex Corp.
PAXIL (paroxetine)	NDA-020710	Suspension, For Oral use	Apotex Technologies, Inc.
PAXIL CR (paroxetine)	NDA-020936	Tablet, for Oral use	Apotex Technologies, Inc.
PEXEVA (paroxetine mesylate)	NDA-021299	Tablet, for Oral use	Sebela Pharmaceuticals, Inc.
ZOLOFT (sertraline hydrochloride)	NDA-019839	Tablet, for Oral use	Upjohn US 1 LLC
ZOLOFT (sertraline hydrochloride)	NDA-020990	Solution, for Oral use	Upjohn US 1 LLC
citalopram hydrobromide	NDA-021763	Tablet, for Oral use	Biovail International, LLC
CELEXA (citalopram hydrobromide)	NDA-021046	Solution, for Oral use	Forest Laboratories I
CELEXA (citalopram hydrobromide)	NDA-020822	Tablet, for Oral use	Allergan Sales LLC
LEXAPRO (escitalopram oxalate)	NDA-021365	Solution, for Oral use	Allergan Sales LLC
LEXAPRO (escitalopram oxalate)	NDA-021323	Tablet, for Oral use	Allergan Sales, LLC
VIIBRYD (vilazodone hydrochloride	NDA-022567	Tablet, for Oral use	Allergan Sales, LLC
TRINTELLIX (vortioxetine)	NDA-204447	Tablet, for Oral use	Takeda Pharmaceuticals USA
SARAFEM (fluoxetine hydrochloride)	NDA-021860	Tablet, for Oral use	Allergan Pharmaceuticals International LTD

1 INTRODUCTION

This review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Psychiatry (DP) and the Division of Urology, Obstetrics, and Gynecology (DUOG) on April 16, 2021 and April 28, 2021, respectively, and May 10, 2021, respectively, for DMPP and OPDP to align the language in the Medication Guides (MGs) with the DP and DUOG proposed Safety Labeling Change(s) made to the Prescribing Information (PI) in response to post marketing reports in the FDA Adverse Event Reporting System (FAERS) and biomedical literature that suggest an association between the use of selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) and the occurrence of sexual dysfunction.

The U.S. Food and Drug Administration (FDA) intends to approve a labeling change common to all class members on the same day, consequently, the suggested MG language pertains to all SSRI and SNRI class MGs.

2 MATERIAL REVIEWED

- Draft proposed SSRI and SNRI Sexual Dysfunction Safety Labeling Change (SLC) Prescribing Information (PI) language received by DMPP and OPDP on May 7, 2021.

3 REVIEW METHODS

In our safety labeling change review, we:

- simplified wording and clarified concepts where possible
- ensured that the proposed MG language is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the proposed SLC MGs language is consistent with the proposed Prescribing Information (PI)

4 RECOMMENDATIONS

- Please send this proposed MG language to the Applicant and copy DMPP and OPDP on the correspondence.
- Consult DMPP and OPDP during the next review cycle for a comprehensive review of the Patient Labeling.
- Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MGs.
- Please let us know if you have any questions.

The DMPP-OPDP proposed MG language is:

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/s/

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR PATIENT LABELING REVIEW CONSULTATION

TO: **CDER-DMPP-PatientLabelingTeam**
CDER-DMPP-PatientLabelingTeam@fda.hhs.gov

FROM: (Name/Title, Office/Division/Phone number of requestor)
HFD-130/ Division of Psychiatry (DP)
Ermias Zerislassie SRPM

REQUEST DATE:
4/16/2021

NDA NO:

SNRI
NDA-021992
NDA-204683
NDA-204150
NDA-204168
NDA-021427
NDA-020699
NDA-022104
NDA-212516

SSRI
NDA 204447
NDA-018936
NDA-202133
NDA-020031
NDA-020710
NDA-020936
NDA-021299
NDA-019839
NDA-020990
NDA-020822
NDA-021365
NDA-021323
NDA-022567

TYPE OF DOCUMENTS:
(PLEASE CHECK OFF BELOW)

NAME OF DRUG:
See "NDA NO" section

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG: SSRI/SNRI

DESIRED COMPLETION DATE
(Generally 2 Weeks after receiving substantially complete labeling)
5/07/2021

SPONSOR: Multiple

PDUFA Date: N/A
Class Safety Labeling Change planned for May 2021

TYPE OF LABEL TO REVIEW

TYPE OF LABELING:
(Check all that apply)
- ☐ PATIENT PACKAGE INSERT (PPI)
- ☒ MEDICATION GUIDE
- ☐ INSTRUCTIONS FOR USE(IFU)

TYPE OF APPLICATION/SUBMISSION
- ☐ ORIGINAL NDA/BLA/ANDA
- ☐ LABELING EFFICACY SUPPLEMENT
- ☐ SAFETY SUPPLEMENT
- ☐ LABELING SUPPLEMENT
- ☐ MANUFACTURING (CMC) SUPPLEMENT
- ☐ PLR CONVERSION

REASON FOR LABELING CONSULT
- ☐ INITIAL PROPOSED
- ☐ LABELING REVISION

- **SP link to drafted labeling language: DP SSRI/SNRI/NRI Sexual Dysfunction draft labeling language**
- **Last approved labels/MG:** Last approved labels SSRI and SNRI

Please Note: DMPP uses substantially complete labeling, which has already been marked up by the CDER Review Team, when reviewing MedGuides, IFUs, and PPIs. Once the substantially complete labeling is received, DMPP will complete its review within 14 calendar days. Please provide a copy of the sponsor's proposed patient labeling in Word format.

COMMENTS/SPECIAL INSTRUCTIONS:

1. DP, DUOG, DAPP, and OGD are working on language to incorporate sexual dysfunction into SSRI/SNRI labeling. A class SLC request is planned for May 2021.

   DP requests your expertise to develop language consistent with the proposed labeling language (see SP link
2. above) for MGs across the class.
3. We note that this consult request references NDAs under DP purview. Separate consults will be submitted for NDAs under DUOG and DAPP.
4. POC: Kimberly Updegraff, DP/ADL

SIGNATURE OF REQUESTER
Ermias Zerislassie

Version: 06/06/2016

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